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(54) Title: THE USE OF THE COMBINATION OF CICLESONIDE AND ANTIHISTAMINES FOR THE TREATMENT OF ALLERGIC RHINITIS

(57) Abstract: The present invention relates to a combination of ciclesonide with antihistamines.

THE USE OF THE COMBINATION OF CICLESONIDE AND ANTIHISTAMINES FOR THE TREATMENT OF ALLERGIC RHINITIS

Technical Field of the Invention

The present invention is related to a novel combination of ciclesonide and antihistamines for use in drug therapy in particular in the treatment of allergic rhinitis. In particular the novel combination is administered in the form of an aqueous pharmaceutical composition that contains ciclesonide and antihistamine and having an osmotic pressure of less than 290 mOsm.

Background Art

Allergic rhinitis is a common disorder and the number of patients is steadily increasing. The disease is caused by ambient airborne allergens, which cause an allergic inflammation within the nasal mucosa and it is often accompanied by conjunctivitis. According to the allergen, the allergic rhinitis is subdivided into seasonal allergic rhinitis (allergens like grass pollen, cedar pollen) and perennial allergic rhinitis (indoor allergens like mould, allergens from animals and house dust mite). Allergic rhinitis has a great impact on the quality of life. The patients suffer from an itchy and running nose, nasal blockage, headache and fatigue. Allergic conjunctivitis is often linked to allergic rhinitis and requires co-treatment. The major symptoms of conjunctivitis are burning and itching eyes and lacrimation. The basic mechanisms involved in this disease are the same as for allergic rhinitis.

The current treatment of allergic rhinitis is mainly focused on symptomatic relief. Oral and to a lesser extent topical antihistamines are the most widely used remedies. Oral antihistamines alleviate the histamine driven symptoms only. Allergen contact causes degranulation of mucosal mast cells and histamine is released. Histamine is responsible for the itching and sneezing and the increase in nasal secretion. Antihistamines block the binding of histamine to the histamine-H1-receptor and thereof the histamine mediated symptoms. Beside this obvious pathway, the allergens cause an eosinophilic inflammation of the nasal mucosa, which is mainly responsible for symptoms like nasal hyperreactivity, nasal blockage and the fear of the so called change of floors, which means that an untreated allergic rhinitis can develop to sinusitis and asthma bronchiale.

Treatment with glucocorticoids is currently the only one therapy, which targets the underlying allergic inflammation. To avoid systemic side effects typically for glucocorticoids, e.g. immunosuppression, reduced protein synthesis, impaired growth in children, topical treatment with glucocorticoids is the preferred way of administration.

A disadvantage of nasal steroids is the slow onset of action and the need for continuous treatment. It takes 4-6 days of continuous treatment before a symptom relief can be observed. Therefore, the pa-

tients are recommended to begin to take glucocorticoids before the pollen season starts. The slow onset of action, the need of consequent treatment and the fear of steroid induced side effects have a negative impact on the use of intranasal steroids and patient's compliance.

Other medications available for the treatment are just for symptomatic relief, for example intranasal muscarinic antagonists (ipratropium to reduce nasal secretion), adrenoreceptor agonists (xylometha-zoline to reduce nasal congestion).

WO 97/01337 describes a nasal spray or nasal drops formulation comprising beclomethasone, flunisolide, triamcinolone, dexamethasone or budesonide in combination with the antihistamines levocabastine, azelastine or azatadine and sterile water.

WO 97/46243 is related to a nasal spray containing an intranasal steroid and an antihistamine.

WO 98/48839 is related to topically applicable nasal compositions comprising a therapeutically effective amount of an antiinflammatory agent and a therapeutically effective amount of at least one agent selected from the group consisting of a vasoconstrictor, a neuraminidase inhibitor, a leukotriene inhibitor, an antihistamine, an antiallergic agent, an anticholinergic agent, an anesthetic and a mucolytic agent.

WO 01/22955 is related to a novel combination of loteprednol, a so-called soft steroid with antihistamines.

WO 03/049770 discloses compositions and methods for treating rhinitis with H1 antagonists/antiallergics and safe steroids.

US 5164194 is related to nasal formulations for azelastine.

Detailed Description of the invention

Surprisingly it has now been found that combined administration of ciclesonide and at least one antihistamine results in a very effective and safe treatment of symptoms accompanied with allergic rhinitis and/or allergic conjunctivitis. In particular by combined administration of the ciclesonide and the antihistamine as hypotonic aqueous pharmaceutical formulation a rapid onset of action and quick symptom relief is observed without the fear of glucocorticoid like side effects. By administering such hypotonic aqueous pharmaceutical composition according to the invention to the nasal mucosa the active ingredients rapidly enter the nasal mucosa and have a very long retention time. Therefore very low doses of ciclesonide and a once-daily, maximal twice-daily treatment is necessary to achieve an effective treatment.

In one aspect the present invention therefore relates to the combined administration of ciclesonide and at least one antihistamine for the treatment of allergic rhinitis and/or allergic conjunctivitis. Another subject of the invention therefore is a pharmaceutical composition for the treatment of allergic rhinitis and/or allergic conjunctivitis comprising as active ingredients a combination of at least one antihistamine, a pharmaceutically acceptable salt and/or a solvate or physiologically functional derivative thereof and ciclesonide, pharmaceutically acceptable salts of ciclesonide, epimers of ciclesonide in any mixing ratio with ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof and a pharmaceutically acceptable carrier and/or one or more excipients.

It will be appreciated that the compounds of the combination may be administered simultaneously, either in the same pharmaceutical formulation (hereinafter also referred to as fixed combination) or in different pharmaceutical formulations (hereinafter also referred to as free combination) or sequentially in any order. If there is sequential administration, the delay in administering the second compound should not be such as to lose the beneficial therapeutic effect of the combination. As an example, both drugs may be provided separately as oral formulations, or one may be an oral preparation and the other an inhalant, or both may be provided in a form suitable for application to mucosa (nasal application). Administration may be at the same time. Or they may be administered either close in time or remotely, such as where one drug is administered in the morning and the second drug is administered in the evening.

Accordingly, the present invention also provides a method for the prophylaxis or treatment of allergic rhinitis and/or allergic conjunctivitis in a mammal, such as a human, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising at least one antihistamine or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof and ciclesonide or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutical acceptable carrier and/or one or more excipients. In a preferred aspect, there is provided such a method, which comprises administration of a therapeutically effective amount of a combination comprising at least one antihistamine and ciclesonide, and a pharmaceutical acceptable carrier and/or one or more excipients.

The formulations include those suitable for oral, parenteral including subcutaneous, intradermal, intramuscular, intravenous and intraaarticular, intranasal, inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular administration) although the most suitable route may depend upon for example the condition and disorder of the recipient. In a preferred embodiment according to the invention the formulation is suitable for topical administration. In a preferred embodiment the formulation according to the invention is a formulation suitable for application to mucosa in the case of treatment of allergic rhinitis. In the case of treatment of allergic conjunctivitis a preferred formulation is a formulation suitable for conjunctival administration (application to the conjunctival sac). The formulations may conveniently be presented in unit dosage form and may

be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredients into association with the carrier, which constitutes one or more accessory ingredients/excipients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

In a preferred embodiment the present invention relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa, comprising as active ingredients a combination of at least one antihistamine and ciclesonide. In particular the aqueous pharmaceutical composition is a sterile aqueous pharmaceutical composition.

The present invention further relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa comprising as active ingredients a combination of at least one antihistamine and ciclesonide together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm. Preferably the osmotic pressure is 150 mOsm or lower, more preferably 72 mOsm or lower, more preferably 60 mOsm or lower, more preferably 40 mOsm or lower, more preferably 30 mOsm or lower and still more preferably 20 mOsm (e.g. 10 mOsm or lower).

According to the present invention it is not particularly required to add a substance for controlling osmotic pressure (osmotic pressure-controlling agent) but when it is added any substance can be used. In the present invention, a substance for controlling osmotic pressure (osmotic pressure controlling agent) can be added to control osmotic pressure, specific examples of which include salts such as sodium chloride and water-soluble sugars such as glucose, with glucose being a particularly preferable example.

In a preferred embodiment the pharmaceutical composition is a pharmaceutical composition as described for ciclesonide in WO 01/28562 or WO 01/28563.

Thus in one aspect the present invention relates to an aqueous pharmaceutical composition for the treatment of allergic rhinitis for application to the mucosa, comprising as active ingredients a combination of at least one antihistamine and ciclesonide together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm.

The water-insoluble or water-low soluble substance may be any substance, and preferred examples include celluloses, more preferably crystalline celluloses and particularly preferred microcrystalline celluloses. According to the present invention, the concentration of water-insoluble and/or water-low soluble substance present in form of solid particles in an aqueous medium is preferably 0.3% w/w and above, and particularly preferably 0.5% w/w to 5% w/w, relative to the total amount of the composition.

In addition, an aqueous polymer substance can also be added in the present pharmaceutical composition. Specific examples of such include propylene glycol alginate, pectin, low methoxyl pectin, gua gum, gum Arabic, carrageenan, methyl cellulose, carboxymethyl cellulose sodium, xanthan gum hydroxypropylmethyl cellulose and hydroxypropyl cellulose, while particularly preferable examples include carboxymethyl cellulose sodium, polyethylene glycol and hydroxypropyl cellulose. Carboxymethyl cellulose sodium blended with microcrystalline cellulose, is an example of a combination of these water-soluble substance and water-insoluble substance that can be used in the present invention. Furthermore, in the case of adding these water-soluble polymer substances, the concentration of said substance is preferably 1% w/w to 30 % w/w relative to the water-insoluble substance and/or water-low soluble substance.

In a preferred embodiment of the invention hydroxypropylmethyl cellulose is contained in the pharmaceutical compositions according to the invention. The hydroxypropylmethyl cellulose may be any grade, a specific example is hydroxypropylmethyl cellulose 2910. Although said hydroxypropylmethyl cellulose may be present at any concentration, its concentration is preferably from 0.001 % w/w to 30 % w/w, particularly preferably form 0.01 % w/w to 5 % w/w, more particularly preferably from 0.01 % w/w to 1 % w/w, and most preferably from 0.01 % w/w to 0.5 % w/w, relative to the total amount of composition.

A surfactant and/or wetting agent, although not essential in the present invention, can be added, specific examples of which include Polysorbate 80, glycerin monosterarate, polyoxyl stearate, lauromacrogol, sorbitan oleate and sucrose fatty acid esters.

An effective amount of ciclesonide and the topical antihistamine used in the present invention can be determined according to the type and degree of the respective disease, as well as the age and body weight of the patient, and so forth. Preferably the pharmaceutical composition according to the invention is administered as one to four sprays per nostril once or twice a day. The dose of ciclesonide per actuation is expediently from 10 µg to 400 µg, preferably 20 µg to 200 µg. The dose of the antihistamine per actuation will depend on the type of antihistamine and the route of administration. Expediently the dose is from 10 µg to 500 µg, preferably 25 µg to 250 µg per actuation. In case of azelastin the dose preferably is within the ranges described in US 5164194.

Ciclesonide (hereinafter also referred to as active ingredient) is the INN for a compound with the chemical name [11β,16α(R)]-16,17-[(Cyclohexylmethylen)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)pregna-1,4-dien-3,20-dion. Ciclesonide and its preparation are disclosed in DE 4129535. Ciclesonide as used herein also includes, pharmaceutically acceptable salts of ciclesonide, epimers of ciclesonide (e.g. [11β,16α(S)]-16,17-[(Cyclohexylmethylen)bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-pregna-1,4-dien-3,20-dion) in any mixing ratio with ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof. By the term "physiologically functional derivative" is meant a chemical derivative of ciclesonide having the same physiological function as ciclesonide, for example, by being convertible in the body thereto or by being an active metabolite of ciclesonide.

ide. Physiological functional derivatives of ciclesonide which may be mentioned in connection with the invention are for example the 21-hydroxy derivative of ciclesonide with the chemical name 16α ,17-(22R,S)-Cyclohexylmethylendioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion, 16α,17-(22S)-Cyclohexylmethylendioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion and in particular 16α ,17-(22R)-Cyclohexylmethylendioxy-11β,21-dihydroxypregna-1,4-dien-3,20-dion. This compound and its preparation are disclosed in WO 9422899.

Preferably ciclesonide is dispersed in the aqueous medium in form of solid particles.

The concentration of ciclesonide of the present invention is preferably from 0.01 % w/w to 1 % w/w, and particularly preferably from 0.05 w/w to 0.5 % w/w, relative to the total amount of the composition.

Although the ciclesonide particles that can be used in the present invention may be of any size, they are preferably within the range of 10 nm to 100 µm, and particularly preferably within the range of 100 nm to 10 µm.

Antihistamines, which may be mentioned in connection with the invention, can be any antihistamine suitable for the treatment of allergic rhinitis and/or allergic conjunctivitis. Examples which may be mentioned are (E)-6-[(E)-3-(1-pyrrolidinyl)-1-p-tolylpropenyl]-2-pyridineacrylic acid [INN: ACRIVASTINE], 6,11-Dihydro-11-(1-methyl-4-piperidyliden)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridin [INN: AZATADINE], 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)phthalazinone [INN: AZELASTINE], (+)-(S)-4-[4-[1-(4-chlorophenyl)-1-(2-pyridyl)methoxy]piperidin-1-yl]-butanoic acid [INN: BEPOTASTINE], (plus/minus)-[2-[4-(p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: CETIRIZINE], (+)-2-{2-[(p-Chlor-alpha-methyl-alpha phenylbenzyl)oxy]ethyl}-1-methylpyrrolidin [INN: CLEMASTINE], 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridine [INN: DESLORATADINE], [3-(4-Chlorophenyl)-3-pyridin-2-yl-propyl]-dimethylamine [INN: DEXCHLORPHENIRAMINE], 4'-tert-butyl-4-[4-(diphenylmethoxy)piperidino]butyrophenone [INN: EBASTINE], [2-[4-[bis(p-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid [INN: EFLETIRIZINE], 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-benzimidazole [INN: EMEDASTINE], 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine [INN: EPINASTINE], (plus/minus)-p-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidino]-butyl]-alpha-methylhydratropic acid [INN: FEXOFENADINE], 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)-piperidin-1-yl]propionic acid [Research Code: HSR-609], (-)-(3S,4R)-1-[cis-4-cyano-4-(p-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid [INN: LEVOCABASTINE], [2-[4-[(R)-p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: LEVOCETIRIZINE], ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate [INN: LORATADINE], 2-[N-[1-(4-fluorobenzyl)-1H-benzimidazol-2-yl]-4-piperidinyl]-N-methyl-amino]pyrimidin-4(3H)-one [INN: MIZOLASTINE], 1-(4-fluorobenzyl)-2-(piperidin-4-ylamino)-1H-benzimidazole [INN: NORASTEMIZOLE], 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methyl-1-propanamine [INN: NORTRIPTYLINE], 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one [INN: PEMIROLAST], 8-chloro-11-[1-(5-methylpyridin-3-ylmethyl)piperidin-4-yl-

idene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine [INN: RUPATADINE], 1-[2-[(p-chloro-alpha-methyl-alpha-phenylbenzyl)oxy]ethyl]hexahydro-1H-azepine [INN: SETASTINE], S-(7-carboxy-4-hexyl-9-oxoxanthen-2-yl)-S-methylsulfoximine [INN: SUDEXANOX], 1-(p-tert-butylphenyl)-4-[4'-(alpha-hydroxydiphenylmethyl)-1'-piperidyl]-butanol [INN: TERFENADINE], N-benzyl-N,N'-dimethyl-N-(2-pyridyl)-ethylenediamine [INN: TRIPELENAMINE] and 1-(4-fluorobenzyl)-2-(piperidin-4-ylamino)-1H-benzimidazole [INN: TECASTEMIZOLE] and mixtures thereof. The antihistamine may also be present in form of a pharmaceutically acceptable salt and/or a solvate. Depending on the chemical structure the antihistamine may exist in different stereoisomeric forms. The term antihistamine includes the pure stereoisomers (eg. pure epimer, diastereoisomer or enantiomer) and their mixtures in any mixing ratio. Suitable pharmacologically acceptable salts of antihistamines are in particular water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid, the acids being employed in salt preparation – depending on whether it is a mono- or polybasic acid and depending on which salt is desired – in an equimolar quantitative ratio or one differing therefrom. By the term "physiologically functional derivative" is meant a chemical derivative of an antihistamine having the same physiological function as the antihistamine, for example, by being convertible in the body thereto or by being an active metabolite of the antihistamine. In a preferred embodiment the antihistamine is an antihistamine with long acting topical activity. Azatadine, azelastin, levocabastin and pharmaceutically acceptable salts thereof are particularly preferred. Azatadine is known e.g. from US 3326924. Preferred salts of azatadine include its maleate, sulfate, succinate and acetate salts. Azelastine is known from US 3813384 and from US 5164194. Preferred are acid addition salts, such as, the hydrohalogen salt and salts with organic acids. Preferred salts include the hydrochloride, hydrobromide, salts with embonic acid, maleic acid, citric acid and tartaric acid. Levocabastine is known from US 4369184. Suitable salts include the hydrochloride, hydrobromide and salts with sulphuric acid, nitric acid, acetic acid and propionic acid.

In case of water soluble antihistamines such as azelastin hydrochloride, the antihistamine will be dissolved in the pharmaceutical compositions according to the invention.

The concentration of the topical antihistamine is preferably from 0.01 % w/w to 0.5 % w/w, and particularly preferably from 0.05 w/w to 0.2 % w/w, relative to the total amount of the composition.

Any method for dispersing a water-insoluble substance and/or water-low soluble substance in an aqueous medium may be used for the production of the aqueous pharmaceutical composition according to the invention, a specific example of which is a method that uses a homomixer.

Known antiseptics, pH controlling agents, preservatives, buffers, colorants, smell corrigents and so forth may be added as necessary to the compositions of the present invention to improve its physical properties, stability, appearance or odor and so forth of the formulation.

Examples of antiseptics include benzalkonium chloride, examples of pH controlling agents include hydrochloric acid and sodium hydroxide, examples of preservatives include potassium sorbate, examples of buffers include phosphoric acid and its salt, examples of colorants include red dye no. 2, and examples of smell corrigents include menthol.

Due to the unique galenic formulation, ciclesonide rapidly enters the nasal mucosa and has a very long retention time. Therefore, very low doses of ciclesonide and the once daily, maximal twice-daily treatment is necessary to achieve an effective treatment. A low dose of ciclesonide in a hypotonic watery suspension in combination with a topical antihistamine (e.g. azelastine or levocabastine) results in a very effective and safe treatment of all symptoms accompanied with allergic rhinitis. A clear advantage of this combination is the rapid onset of action and quick symptom relief without the fear of glucocorticoid like side effects.

In another embodiment the present invention relates to a combination of ciclesonide with azelasine and ciclesonide is applied in a pharmaceutical composition as described for ciclesonide in WO 01/28562 or WO 01/28563 and azelastine is applied in a pharmaceutical formulation according to US 5164194.

When given to the nasal mucosa the formulation according to the present invention may be filled into plastic squeeze bottles or plastic or glass bottles, which are fitted with a metering atomising pump and a nasal adapter or with a suitable dropper. When given to the eye the formulation according to the present invention may be filled into plastic squeeze bottles or plastic or glass bottles, which are fitted with a suitable dropper.

Examples

Ciclesonide aqueous pharmaceutical compositons containing the components indicated below are prepared by processing with a homomixer. Homomixer processing is performed, e.g., at 6000 rpm for 30 minutes.

Example 1: Combination of Ciclesonide and Azelastine Hydrochloride

Ciclesonide:	0.05%
Azelastine hydrochloride	0.14%
Microcrystalline cellulose and carboxymethyl cellulose sodium	1.7%
Hydroxypropylmethyl cellulose 2910	0.1%

Each 100 mg spray delivered by a nasal applicator delivers 50 µg of ciclesonide and 140 µg of azelastine hydrochloride.

Example 2: Combination of Ciclesonide and Levocabastine Hydrochloride

Ciclesonide:	0.05%
Levocabastine hydrochloride	0.054%
Microcrystalline cellulose and carboxymethyl cellulose sodium	1.7%
Hydroxypropylmethyl cellulose 2910	0.1%

Each 100 mg spray delivered by a nasal applicator delivers 50 µg of ciclesonide and 54 µg of levocabastine hydrochloride (equivalent to 50 µg levocabastine).

Patent Claims

1. Pharmaceutical composition for the treatment of allergic rhinitis and/or allergic conjunctivitis comprising as active ingredients a combination of at least one antihistamine, a stereoisomer, a Pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof and ciclesonide, pharmaceutically acceptable salts of ciclesonide, epimers of ciclesonide optionally in any mixing ratio with ciclesonide, solvates of ciclesonide, physiologically functional derivatives of ciclesonide or solvates thereof and a pharmaceutically acceptable carrier and/or one or more excipients.

2. Pharmaceutical composition according to claim 1 for the treatment of allergic rhinitis for application to the mucosa, which is an aqueous pharmaceutical composition comprising the active ingredients together with one or more water-insoluble and/or water-low soluble substance and having an osmotic pressure of less than 290 mOsm.

3. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 150 mOsm or less.

4. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 60 mOsm or less.

5. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 40 mOsm or less.

6. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said osmotic pressure is 20 mOsm or less.

7. The pharmaceutical composition for application to the mucosa according to claim 2, further comprising an osmotic pressure-controlling agent.

8. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said water-insoluble and/or water-low soluble substance is a cellulose.

9. The pharmaceutical composition for application to the mucosa according to claim 8, wherein said cellulose is microcrystalline cellulose.

10. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said one or more water-insoluble and/or water-low soluble substance is present as solid particles in an aqueous medium.

11. The pharmaceutical composition for application to the mucosa according to claim 2, further comprising a water-soluble polymer substance.

12. Pharmaceutical composition for application to the mucosa according to claim 11, wherein a combination of said water-insoluble substance and water-soluble polymer is present which is microcrystalline cellulose and carboxymethyl cellulose sodium.

13. The pharmaceutical composition for application to the mucosa according to claim 2, further comprising a surfactant and/or a wetting agent.

14. The pharmaceutical composition for application to the mucosa according to claim 2, wherein said mucosa is nasal mucosa.

15. Pharmaceutical composition according to claims 1 through 14, wherein the antihistamine is selected from the group of (E)-6-[(E)-3-(1-pyrrolidinyl)-1-p-tolylpropenyl]-2-pyridineacrylic acid [INN: ACRIVASTINE], 6,11-Dihydro-11-(1-methyl-4-piperidyliden)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridin [INN: AZATADINE], 4-[(4-chlorophenyl)methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)phthalazinone [INN: AZELASTINE], (+)-(S)-4-[4-[1-(4-chlorophenyl)-1-(2-pyridyl)methoxy]piperidin-1-yl]-butanoic acid [INN: BEPOTASTINE], (plus/minus)-[2-[4-(p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: CETIRIZINE], (+)-2-(2-[(p-Chlor-alpha-methyl-alpha phenylbenzyl)oxy]-ethyl)-1-methylpyrrolidin [INN: CLEMASTINE], 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridine [INN: DESLORATADINE], [3-(4-Chlorophenyl)-3-pyridin-2-yl-propyl]-dimethylamine [INN: DEXCHLORPHENIRAMINE], 4'-tert-butyl-4-[4-(diphenylmethoxy)-piperidino]butyrophenone [INN: EBASTINE], [2-[4-[bis(p-fluorophenyl)methyl]-1-piperazinyl]ethoxy]-acetic acid [INN: EFLETIRIZINE], 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1H-1,4-diazepin-1-yl)-benzimidazole [INN: EMEDASTINE], 3-amino-9,13b-dihydro-1H-dibenz[c,f]imidazo[1,5-a]azepine [INN: EPINASTINE], (plus/minus)-p-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidino]-butyl]-alpha-methylhydratropic acid [INN: FEXOFENADINE], 3-[4-(8-fluoro-5,11-dihydrobenz[b]oxepino[4,3-b]pyridin-11-ylidene)-piperidin-1-yl]propionic acid [Research Code: HSR-609], (-)-(3S,4R)-1-[cis-4-cyano-4-(p-fluorophenyl)cyclohexyl]-3-methyl-4-phenylisonipecotic acid [INN: LEVOCABASTINE], [2-[4-[(R)-p-chloro-alpha-phenylbenzyl)-1-piperazinyl]ethoxy]-acetic acid [INN: LEVOCETIRIZINE], ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate [INN: LORATADINE], 2-[N-[1-(4-fluorobenzyl)-1H-benzimidazol-2-yl]-4-piperidinyl]-N-methyl-amino]pyrimidin-4(3H)-one [INN: MIZOLASTINE], 1-(4-fluorobenzyl)-2-(piperidin-4-ylamino)-1H-benzimidazole [INN: NORASTEMIZOLE], 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-N-methyl-1-propanamine [INN: NORTRIPTYLINE], 9-methyl-3-(1H-tetrazol-5-yl)-4H-pyrido[1,2-a]pyrimidin-4-one [INN: PEMIROLAST], 8-chloro-11-[1-(5-methylpyridin-3-ylmethyl)-piperidin-4-ylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine [INN: RUPATADINE], 1-[2-[(p-chloro-alpha-methyl-alpha-phenylbenzyl)oxy]ethyl]hexahydro-1H-azepine [INN: SETASTINE],

S-(7-carboxy-4-hexyl-9-oxoxanthen-2-yl)-S-methylsulfoximine [INN: SUDEXANOX], 1-(p-tert-butyl-phenyl)-4-[4'-(alpha-hydroxydiphenylmethyl)-1'-piperidyl]-butanol [INN: TERFENADINE], N-benzyl-N,N'-dimethyl-N-(2-pyridyl)-ethylenediamine [INN: TRIPELENAMINE] and 1-(4-fluorobenzyl)-2-(piperidin-4-ylamino)-1H-benzimidazole [INN: TECASTEMIZOLE] and mixtures, stereoisomers thereof, pharmaceutically acceptable salts and/or solvates thereof.

16. Pharmaceutical composition according to claims 1 through 14, wherein the antihistamine is azelastine, levocabastine, a salt or solvate thereof.

17. Use of ciclesonide in combination with at least one antihistamine for the manufacture of a pharmaceutical composition for the treatment of allergic rhinitis and/or allergic conjunctivitis.

18. Method for the prophylaxis or treatment of allergic rhinitis and/or allergic conjunctivitis in a mammal, such as a human, which comprises administration of a therapeutically effective amount of a pharmaceutical formulation comprising at least one antihistamine or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof and ciclesonide or a pharmaceutical acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutical acceptable carrier and/or one or more excipients.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/09622

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/58 A61P37/08 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 12235 A (KATO TOMOKI ;PFIZER PHARMA (JP); SHISHIDO YUJI (JP); IKEDA TAKAFUM) 14 February 2002 (2002-02-14) claim 18 page 25, line 31 page 23, line 19 - line 31 ---	1,15
X	US 2002/115680 A1 (PIEPER MICHAEL PAUL ET AL) 22 August 2002 (2002-08-22) page 12, paragraph '0174! page 12, paragraph '0177! page 13, paragraph '0179! ---	1,15
Y	WO 01 28562 A (NISHIBE YOSHIHISA ;NAGANO ATSUHIRO (JP); TEIJIN LTD (JP); TAKANASH) 26 April 2001 (2001-04-26) claims 1-23 ---	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 November 2003	20/11/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Beranová, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/09622

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SCHMIDT BERNHARD M W ET AL: "The new topical steroid ciclesonide is effective in the treatment of allergic rhinitis" JOURNAL OF CLINICAL PHARMACOLOGY, vol. 39, no. 10, October 1999 (1999-10), pages 1062-1069, XP008024248 ISSN: 0091-2700 * page 1062, abstract *	1-18
Y	EP 0 903 151 A (ASTA MEDICA AG) 24 March 1999 (1999-03-24) * page 2, paragraphs '0002!, '0006! and '0007! *	1-18
Y	MATTILA MAURI J ET AL: "Variations among non-sedating antihistamines: Are there real differences?" EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, vol. 55, no. 2, April 1999 (1999-04), pages 85-93, XP002260456 ISSN: 0031-6970 page 90, left-hand column -page 91, left-hand column	1-18

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 - 14 and 16 - 18 relate to compounds defined by reference to a desirable characteristic or property, namely "antihistamine" and "osmotic pressure-controlling agent". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds listed in claim 15 in combination with ciclesonide.
Furthermore, present claims 1 - 14 and 16 - 18 relate to an extremely large number of possible compounds ("functional derivatives thereof" and "water soluble polymer substance") resulting in a lack of disclosure within Article 5 PCT.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/09622

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/09622

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			CA	2418908 A1	14-02-2002
			EP	1307449 A1	07-05-2003
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